

## ALTERNATIVES

### **4.1 Definitions:**

**Alternatives:** Methods, models, and approaches that result in the reduction of the number of animals required, that incorporate refinements of procedures which result in the lessening of pain or distress to animals, or that provide for the replacement of animals with non-whole animal systems or the replacement of one animal species with another, particularly if the substituted species is non-mammalian or invertebrate. (Stokes 1995)

**Biomedical Model:** A surrogate system, either animate or inanimate that mimics or is predictive about a biologic process or condition of interest

### **4.2 Principle for the Use of Alternatives:**

**The Three R's:** As described by W. M. S. Russell and R. L. Burch, 1959.

**Replacement:** Substitution of insentient material for animals or substitution of a lower species, which might be less sensitive to pain and distress, for a higher species.

**Reduction:** Reduction in the numbers of animals used to obtain information of a certain amount and precision.

**Refinement:** Decrease in the incidence or severity of pain and distress in those animals that are used.

### **4.3 Rationale for Considering Alternatives:**

**Regulatory:** Animal Welfare Act regulations specify that:

Principal investigators **must** consider alternatives to any procedure likely to produce pain or distress.

Assurance that alternatives have been considered **must** be presented in the institution's annual report and when the institution is inspected by the USDA.

Training **must** be provided by the institution on research or testing methods that minimize or eliminate the use of animals or limit their pain or distress.

The National Agricultural Library in cooperation with the National Library of Medicine **must** provide information that could prevent unintended duplication of experiments and that could reduce or replace the use of animals.

PHS Policy specifies that:

Institutions **must** give assurances satisfactory to the director of NIH that they are making available to scientists, animal technicians, and other personnel instruction or training on availability and use of research or testing methods that limit the use of animals or limit pain and distress (PHS, 1986)

**Institutional Policy:**

Should establish animal care and use protocol form requirements. NIH Manual Chapter 3040-2 specifies the format and content for a standard Animal Study Proposal form that must be used by each ICD.

Assures that protocols are reviewed and approved by the institutional animal care and use committee.

**Ethical Considerations:**

Do the potential results of the project justify its likely effects on the animal? (Tannenbaum, 1989)  
In other words, if the animal will be subjected to pain or distress will the scientific value of the project justify that experience for the animal?

**Humane Considerations:** (OTA, 1986)

Can procedures be modified to prevent or minimize pain and distress?

Can analgesics, anesthetics, tranquilizers, or sedatives be used to provide relief from pain and distress?

Can a less sensitive species be used? This issue can be addressed by using an animal of a lower phylogenetic order that has a less developed nervous system than mammals.

**Economic Considerations:**

What are the costs to purchase, house, and care for the animals?

What are the costs for equipment and supplies for a nonanimal model?

What is the cost for a noninvasive technique such as ultrasound or magnetic resonance imaging?

Have nonanimal alternatives been used to screen compounds for efficacy, thus reducing the number of compounds that require testing in animals?

**Scientific Considerations:**

Does the model reliably and accurately reproduce the process or characteristic being studied?

Is the model readily available to other researchers?

Is the model well characterized in the literature?

**4.4 Nonanimal Research Methods and Models:****Literature Search:**

When the animal is likely to experience pain or distress a literature search for an alternative

procedure **is required** by the Animal Welfare Act Regulations.

A search can be used to avoid unnecessary duplication of research.

Can provide a scientific basis for the choice of a model.

#### **Epidemiological Research:**

Can be used to understand the frequency, distribution, and cause of disease, both infectious and noninfectious, in a given population.

#### **Human Subject Research:**

If morally and legally acceptable, safe, noninvasive methods to test human subjects can replace the use of animals.

#### **Cell, Tissue and Organ Culture:**

Systems derived from humans or animals and then maintained and propagated replace the need to experiment on living animals or reduce the number of animals used.

#### **Chemical Analysis:**

Radiological binding assays and radioimmunoassays can be substituted for bioassays.

#### **Microbiological Systems:**

Ames mutagenicity/carcinogenicity test, which uses Salmonella typhimurium

Recombinant DNA studies of gene control using Escherichia coli

#### **Plants:**

Yeasts, in particular, have been used extensively to study basic molecular mechanisms of interest to cellular and molecular biologists and virologists.

#### **Mathematical Systems:**

Statistical design should be applied to all animal research protocols because it can lead to increases or decreases in the number of animals required in a protocol. The design should include consideration of factors such as statistical power, randomization, and compounding variables.

Computer modeling and analysis can be used to study molecular structure and activity relationships. The models are based on in vivo data expressed in a mathematical equation where parameters can be manipulated to simulate a biological effect.

In vivo systems are required to validate conclusions.

#### **4.5 Factors Influencing Model Selection:**

Scientific considerations (Animal Alternatives Study Task Force, 1988).

Relevancy: Models must have one or more features that resemble the original system.

Reliability: Models must allow investigators to obtain consistent, reproducible results.

Simplicity: Simpler models usually provide fewer variables than a whole human or animal and reduce the complexity that can obscure understanding of a specific process.

Accessibility: Models must be readily available to the research community and permit manipulation using contemporary technology.

#### **Ethical Considerations:**

Consideration should be given to the safety of research personnel and human subjects, conservation of species and humane care and use of animals.

#### **Economic Considerations:**

These should include the purchase of animals, animal maintenance (food, caging, labor), supplies, equipment, facilities, and labor for the conduct of animal research as well as the time required to perform the studies.

#### **4.6 Utilization of Services:**

##### **Extramural:**

When local library searches fail to provide adequate information on sources for alternatives the National Agricultural Library can be consulted. (See Animal Welfare Information Center at section 9.2 in this handbook)

There are several centers for alternatives that can provide information for references. Examples include: The Johns Hopkins Center for Alternatives to Animal Testing; the Rockefeller University Laboratory for In Vitro Toxicologic Assay Development; the Fund for the Replacement of Animals in Medical Experiments (FRAME).

##### **Intramural Sources:**

Consult your ICD laboratory animal veterinarian and staff or the NIH Library.

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Revised: 4-18-94